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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,737	01/30/1998	GERALD P. MURPHY	8511-007	7366

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/016,737	MURPHY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) *25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-24, 26, 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 23-24, 26, 28-37 are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 23, 31-32, 33-37 remain rejected under 35 USC 103(a) as being obvious over Sallusto et al, 1994 (J Exp Med, 179: 1109-1118, of record), in view of Bigotti G et al, 1991 (Prostate, V19, N1, p.73-87), as evidenced by Inaba K et al, 1987 (Journal of experimental medicine (UNITED STATES), 166 (1) p:182-94, of record), for reasons already of record in paper of 06/02/06.

A. The response asserts that Bigotti et al do not teach a prostate antigen to replace the tetanus toxoid of Salluto et al. The response asserts that the Examiner infers that Bigotti et al teach presentation of prostate antigen to immune cells. The response asserts that the teachings of Bigotti et al such as correlation of Langerhans cells (LC) and prostate tumor grade, the expression of class II by LCs and tumor cells, and the dependence of antigen presenting

properties on class II expression, do not infer that human DC when exposed in vitro to a prostate antigen can activate T cells specific to a prostate antigen.

The response asserts that Bigotti et al actually teach away from the claimed invention. The response asserts that if the LCs present in the low grade carcinomas were to present prostate antigen to the immune system, one would expect infiltration of immune cells to those locations. Bigotti et al however teach that mostly macrophages and only small percentage of **LCs** are in close contact with tumor glands, and that LCs are present mostly at the **peripheral border of the tumor** as small aggregates. The response asserts that Bigotti et al concludes that there is no correlation between cytological grade, HLA-class II expression, LCs and lymphoid infiltrate, as the latter is present mostly at the peripheral of tumors as aggregates and did not show close contact with the malignant glands. The response asserts that Bigotti et al instead teach that there is correlation between cytological grade and the presence of macrophage in contact with the tumor. The response asserts that Bigotti et al teach that there is evidence in the art that macrophage play an important role in tumor rejection. The reponse concludes that clearly Bigotti et al correlate tumor rejection and lymphocytic infiltrations with the presence of macrophages and not with the presence of LCs.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, Bigotti et al do not teach away from the claimed invention. Although Bigottie et al teach that there is no correlation between cytological tumor grade and the presence of Langerhans cells in **close contact** with the prostate cancer gland, Bigotti et al **do not teach** that there is no correlation between tumor rejection and Langerhans

cells. Bigotti et al clearly teach that that Langerhans cells are found mainly in low grade prostate cancer, as opposed to higher grades, and represent a good prognostic indicator (abstract, p.85). Bigotti et al teach that in this neoplastic environment, Langerhans cells act as antigen-presenting cells, while HLA II molecule may interact primarily or with the aid of Langerhans cells with macrophages and secondarily with T helper lymphocytes causing expansion of cytotoxic T cells, and enhancement of the antibody response to membrane-bound tumor associated antigens, therefore providing a means for controlling the escape of tumor cells from immune surveillance (p.85, paragraph under Conclusions". From the teaching of Bigotti et al, one would have concluded that Langerhans cells act as antigen presenting cells, presenting prostate cancer antigens to the immune systems, causing cytotoxic T cells expansion and enhancement antibody response to prostate cancer antigens, and thus play an important role in prostate cancer rejection, via eliciting an immune response.

In addition, although Bigotti et al teach that this latter mechanism might be of secondary importance, in view of the paucity of lymphoid tissue within tumors (p.85, last two lines of the paragraph under Conclusions), this teaching actually provides motivation for one to make the prostate cancer antigen presenting cells in vitro to administer to a prostate cancer patient for augmenting or supplementing the numbers of available antigen presenting cells in the patient.

Further, Applicant does not have any evidence that only cancer antigens **directly** on the cancer cells at the prostate cancer glands provide antigens for the antigen presenting cells. It well known that immature dendritic cells, such as Langerhans cells, have the ability to capture antigen and process the antigen and efficiently present **soluble** antigen to specific T cells, as taught by Sallusto et al. Applicant does not have any evidence that said tumor antigen exists only on the

surface of cancer cells directly at the prostate cancer gland, and could not be also present at the peripheral border of the cancer gland, due to for example, the presence of antigens from cell membranes of lysed or necrotic cancer cells. Thus, one cannot conclude from the mere absence of a correlation between cytological grade and the presence of Langerhans cells in **contact** with the prostate cancer gland that there is no correlation between tumor rejection and the presence of Langerhans cells in prostate cancer patients.

In addition, although Bigotti et al teach that macrophages play an important role in tumor rejection, Bigotti et al do not exclude that Langerhans cells also play a role in tumor rejection.

One would have concluded from the teaching of Bigotti et al and Sallusto et al that Langerhans cells are capable of presenting antigens, including prostate cancer antigen, to immune cells, such as T cells, and eliciting an immune response, providing a means for controlling the escape of cancer cells from the immune surveillance, in view of that capturing and presenting antigen is a property of immature dendritic cells, such as Langerhans cells, in vitro and in vivo, as taught by Sallusto et al.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to obtain human, immature dendritic cells, using the method taught by Sallusto et al, and to replace the antigen tetanus toxoid taught by Sallusto et al with a prostate antigen taught by Bigotti et al, for exposure of the prostate antigen to the immature dendritic cells, because the dendritic cells, such as Langherhans' cells, would present prostate antigen to immune cells, and activate specific immune response, and thus, would provide treatment of prostate cancer.

One would have a reasonably expectation of success of making the claimed human dendritic cells, because the immature dendritic cells in vitro, obtained from culture in GM-CSF and interleukin-4, maintain the antigen capturing and processing capacity characteristics of immature dendritic cells *in vivo,* and efficiently present soluble antigen, as taught by Sallusto et al.

B. Concerning the recitation of Stites et al on page 7 of the Office action, the response asserts that the Examiner has not provided a summary or reasoning regarding Stites et al.

The Examiner apologizes for the inadvertent reciting of Stites et al on page 7 of the Office action. Clearly, Stites et al is not intended to be included in the rejection, as shown by its absence in the first paragraph on page 3, which recites the relevant references in the 103 rejection.

C. Concerning activation of CD4+ and CD8+ T cells, the response asserts that the combination of Sallusto et al and Bigotti et al does not suggest that the dendritic cells taught by Sallusto et al and Bigotti et al would activate any T cells, much less CD4+ and CD8+ T cells.

The response has been considered but is not found to be persuasive for the following reasons:

One would have concluded from the teaching of Bigotti et al and Sallusto et al that Langerhans cells are capable of presenting antigens, including prostate cancer antigen, to immune cells, such as T cells, and eliciting an immune response, providing a means for controlling the escape of cancer cells from the immune surveillance, supra.

It is noted that the dendritic cells taught by Sallusto et al, Bigotti G et al, and Stites DP would activate CD4+ and/or CD8+ T cells , because activation of CD4+ and/or CD8+ T cells is a property of dendritic cells, as evidenced by Inaba K et al. Further, although the references do not specifically teach that the dendritic cells activate CD4+ and/or CD8+ T cells, however, the claimed dendritic cells appear to be the same as the dendritic cells taught by the combined art, supra, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

D. Concerning the expectation that the human peripheral blood taught by Sallusto et al is from normal donor individual, the response asserts that the combination of Sallusto et al and Bigotti et al does not suggest that replacing the tetanous toxoid antigen with any other antigen. The response asserts that therefore, there is no teaching or suggestion by Sallusto et al and Bigotti et al of the use of normal or diseased peripheral blood as a source of dendritic cells.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al suggests the composition of the claimed invention, supra. Although Sallusto et al do not explicitly state that the human peripheral blood is from a normal individual, Sallusto et al do not state that the human peripheral blood is from a

diseased individual; and the human peripheral blood taught by Sallusto et al would be expected to be from a normal donor individual.

In the alternative, it would have been obvious to use the peripheral blood from normal healthy donor as a source of immature dendritic cells, to increase the availability of the source of immature dendritic cells, in view of the teaching of Sallusto et al and Bigotti et al.

2. Claim 24 remains rejected under 35 USC 103(a) as being obvious over Sallusto et al, in view of Bigotti G et al, and as evidenced by Inaba et al, supra, and further in view of Cohen, PA et al, 1994 (Cancer Research, 54(4): 1055-8) for reasons already of record in paper of 06/02/06.

The response asserts that the combination of Sallusto et al and Bigotti et al does not teach the composition of the claimed invention. The response asserts that the combined references of Sallusto et al, Bigotti et al, Inaba et al and Cohen et al do not provide incentive to combine the references to use a lysate of prostate cancer.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al and Bigotti et al suggests the composition of the claimed invention, supra.

It would have been obvious to use as prostate antigen, a lysate of prostate cancer cells from a prostate cancer patient, because prostate cancer cells would have several prostate cancer-specific antigens, and because a tumor lysate successfully primes the dendritic cells for inducing antigen-specific proliferation of antitumor CD4+ T cells, as taught by Cohen et al, and further because using tumor lysate would be more convenient, and does not require the extra step of purification of the antigen.

3. Claim 26 remain rejected under 35 USC 103(a) as being obvious by Sallusto et al, in view of Bigotti et al, and as evidenced by Inaba et al, supra, as applied to claim 23, and further in view of Lutz et al (of record), for reasons already of record in paper of 06/02/06.

The response asserts that the combination of Sallusto et al, Bigotti et al and/or Inaba et al does not teach the composition of the claimed invention. The response asserts tha Luz et al do not prove motivation to make the composition of claim 26.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto et al, Bigotti et al, and Inaba et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would enable maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

4. Claims 28-29 remain rejected under 35 USC 103 as being obvious by Sallusto et al, Bigotti et al, Inaba et al, and Cohen et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), for reasons already of record in paper of 06/02/06.

The response asserts that the combination of Sallusto et al, Bigotti et al and/or Inaba et al does not teach the composition of the claimed invention. The response asserts that Taylor et al do not address the teachings of Bigotti et al that the immune response is likely induced in prostate

cancer by macrophages. The response asserts that as such the cited references do not teach the composition of claims 28-29.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto et al, Bigotti et al, Stites, and Cohen et al, using the cryopreservation method taught by Taylor et al, to preserve the previously isolated dendritic cells for later use.

5. Claim 30 remains is rejected under 35 USC 103 as being obvious by by Sallusto et al, Bigotti et al, and Inaba et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), as applied to claim 28, and Lutz et al, of record, for reasons already of record in paper of 06/02/06.

The response asserts that the combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al does not teach or suggest the composition of the claimed invention. The response asserts that Luz et al do not cure the deficiency of the primary references.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto et al, Bigotti et al, Inaba et al and Taylor et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would allow maintainance of dendritic cells *in vitro* for long periods of time; as taught by Luz et al.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
January 29, 2007

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